



IS THE CORONA VIRUS LEFT A LEGACY OF PAIN AND SUFFERING?

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ABSTRACT

Between 2019-2022, Corona virus infected millions of people. Nearly three years still we are struggling to understand the extent of this pandemic. In December 2019, a novel corona virus called SARS-CoV-2 caused a sequence of acute atypical pneumonia in Wuhan, China. In early January 2020, Chinese scientists isolated corona virus from the patients' in Wuhan. The outbreak is supposed to have started at a local seafood/wild animal market. The infecting agent was initially called as novel corona virus (2019-nCoV) but was renamed later as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the clinical disease was called corona virus disease of 2019 (COVID-19). It was primarily started as a zoonotic transmission, but it was later esteemed that human to human transmission plays a great role in pandemic outbreak globally. COVID-19 infection is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded RNA betacoronavirus. The impact of disease affects the lungs, practically every organ in the body is vulnerable to injury caused by the SARS-CoV-2 virus. COVID-19 has affected more than 130 million patients in all age groups. Antibiotics have no role in viral infections. Vaccines are the powerful weapon to fight against Covid. COVID-19 ailment has affected more than 120 million patients in all age groups all over the globe. Certain high-risk groups such as the elderly, human immunodeficiency virus (HIV) patients and those with the front arch of ambulatory are at high risk of severe disease. coronavirus SARS-CoV-2, Molnupiravir, SARS-CoV2 RNA.

INTRODUCTION:

30th January, 2020 declared a public health emergency of international concern. Corona viruses are the largest group of viruses. COVID pandemic has given humanity a strong counter. Almost all countries have been destroyed. Financial system has held up. Many have lost their loving ones.

COVID-19 disease, may lead to respiratory failure and mechanical ventilation (1)

Respiratory failure with mechanical ventilation need was reported in 2.3% up to 33% of the affected patients (2,3)

Recently, however, autopsy studies have been published from throughout the world that have defined diffuse alveolar damage (DAD) as the histopathologic hallmark of severe SARS-CoV-2 infection (4)

Identifying co-infections of more than one respiratory virus can help with understanding the various clinical symptoms, long-lasting effects on health, and appropriate methods of prevention (5)

Hospitalization in children under 3 years of age, following simultaneous infection with RSV and Human metapneumovirus (hMPV) (2) Furthermore, patients with viral respiratory tract coinfections are more likely to be admitted to the hospital than individuals with a single respiratory virus infection (6)

Moreover, due to the similarity of common clinical symptoms of COVID-19 with that of the diseases caused by other respiratory viruses, it has become quite challenging to precisely distinguish SARS-CoV-2 infection from other viral infections (7)

It is thought that co-infection with common respiratory viruses can still occur in individuals infected with other respiratory-specific strains (8) Human infections with zoonotic corona viruses (CoVs), including severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, have raised great public health concern globally (8)

The virus is referred as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is transmitted through respiratory tract and could induce pneumonia (9)

Human infections with zoonotic corona viruses (CoVs), including severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, have raised great public health concern globally (10)

In general, coronaviruses cause widespread respiratory, gastrointestinal, and central nervous system diseases in humans and other animals, threatening human health and causing economic loss (11)

Coronaviruses are capable of adapting to new environments through mutation and recombination with relative ease and hence are programmed to alter host

range and tissue tropism efficiently (12)

The emergence and rapid spread of a novel severe acute respiratory syndrome (SARS)-like coronavirus SARS-CoV-2 is destroying global health and economy (13,14)

Coronavirus entry into host cells is an important determinant of viral infectivity and pathogenesis (15,16).

It is also a major target for host immune surveillance and human intervention strategies (17,18)

SARS-CoV spike needs S1/S2 boundary, such that S1 dissociates and S2 undergoes a dramatic structural change (19,20)

HISTORY:

The virus that was first detected in Wuhan, China, in late 2019 and has set off a global pandemic. Researchers say SARS-CoV-2 originated in bats. SARS-CoV-2 made the jump to humans at one of Wuhan's open-air "wet markets." They're where customers buy fresh meat and fish, including animals that are killed on the spot. Some wet markets sell wild or banned species like cobras, wild boars, and raccoon dogs. Crowded conditions can let viruses from different animals swap genes. Sometimes the virus changes so much it can start to infect and spread among people.

STRUCTURE:

Coronaviruses are large, violently globular molecules with peculiar surface protrusions their size to a great extent fluctuates with 80 to 120 nm. They are surrounded by a number of protein molecules. The envelope is made up of a dual lipid layer, the membrane (M), envelope (E) and spike (S) structural proteins. The E and M protein are the structural proteins and justify its size. The M protein provides the overall shape. It consists of 218 to 263 amino acids. It has three domains, a short N-terminal ectodomain, a triple-spanning transmembrane domain, and a C-terminal endodomain. The C-terminal domain forms a matrix-like lattice. Different species can have either N- or O-linked glycans. The M protein is crucial during budding, and envelope formation. The E proteins are minor structural proteins. They are responsible for virion assembly, and morphogenesis. The spikes are the most distinguishing feature of coronaviruses.

Each spike is about 20 nm long. The S protein has S1 and S2 subunits. S protein is a fusion protein that interferes with the binding and membrane fusion of the virus and host cell.

The S1 subunit forms the head of the spike. The S2 subunit forms the stem of the spike. The virus binds and fuses with the host cell with cathepsin and transmembrane protease serine 2

(TMPRSS2) of the host cell

How corona infects cells:

The Coronavirus enters through the nose or mouth, and reaches the airways. The coronavirus outer spike hooks onto specific receptors on the surface of the cell's of the respiratory tract. COVID-19, hooks on to the ACE2 receptor. Coronaviruses first bind to a cell surface receptor for viral attachment, subsequently enter endosomes, and eventually fuse viral and lysosomal membranes. Then the virus fuses into human cells, and allowing the virus to release the genetic material into the cell. The genetic blueprint of the virus is RNA, acts as a message, and translate it into proteins that make up new virus particles. It has been shown that TMPRSS2 and lysosomal proteases are both important for SARS-CoV-2 entry. The virus hijacks the host cell's functions to produce the components needed for it to create copies of itself. Those components self-assemble into new viruses, which eventually burst from the host cell and go on to infect other cells, either in the original host or in a new host. The protein spikes covering the virus's envelope allow it to bind to receptors on the host cell's lipid membrane, leading to infection and sometimes illness.

Immunopathology:

SARS-CoV-2 has an involuntary orientation by an organism for ACE2-expressing epithelial cells of the respiratory tract with people with severe COVID 19 have symptoms. Clinical laboratory findings of elevated IL 2, IL 7, IL 6, GM-CSF, interferon gamma, monocyte chemo attractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP 1 alpha), and (TNF α) are elevated.

The cytotoxic T cells kill the virus cells and the antibody-producing B cells. SARS-CoV-2, controls the MHC class I and II molecules, which inhibits the T-cell mediated immune responses. COVID-19, patients have lower total lymphocyte counts and higher plasma concentrations of a number of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). CD4+ helper T cells, CD8+ cytotoxic T cells, and natural killer cells are all significantly reduced in patients with severe COVID 19 infections. The pro-inflammatory T cell subsets and cytotoxic T cells are elevated.

COVID-19 disrupts health services in 92% of countries: WHO

According to a survey conducted by the World Health Organization on the impact of the COVID-19 pandemic, disruptions in health services, such as vaccination programs and treatment of diseases like AIDS, have been reported in 92% of the 129 countries. The survey was conducted in November-December last year and revealed that health services were severely impacted and there was little or no improvement from the previous survey done in early 2021, said the health agency.

Corona virus Updates:

With inputs from Dr Monica Vasudev WHO recommends two new drugs for Covid-19 The World Health Organization (WHO) has added two new drugs in the treatment armamentarium of Covid-19, baricitinib and sotrovimab in its eighth update of WHO's living guidelines on therapeutics and COVID-19. Baricitinib, a Janus kinase (JAK) inhibitor, is strongly recommended for patients with severe disease or those who are critically ill with Covid-19. It is recommended to be given with corticosteroids

As the world continues to deal with the Omicron-driven latest coronavirus surge, the World Health Organisation (WHO) has yet again issued a warning regarding countries and governments ignoring the phenomenon of long Covid under the 'guise of living with Covid'.

Vitamin D Deficiency Tied to Severe COVID-19: Study

A new study suggests that individuals with vitamin D deficiency are more prone to develop a severe or critical case of COVID-19. Investigators in Israel assessed vitamin D levels in over 250 patients hospitalized at the Galilee Medical Center with a positive COVID-19 test from April 2020 through February 2021

Covid-19 and pregnancy: High incidence of pregnancy-related complications

A National Institutes of Health (NIH) study has shown greater incidence of pregnancy-related complications in pregnant women with Covid-19. These complications were in addition to the direct deleterious effects of the virus. The retrospective multicenter study from 17 US hospitals involving 2352 pregnant women who were infected with SARS-CoV-2 has been published in the Journal of the American Medical Association.

Higher risk of pregnancy complications in unvaccinated women:

The risk for pregnancy-related complications are higher in the unvaccinated pregnant women with Covid-19, according to a new study from Scotland reported in the journal Nature Medicine. This study has shown that the vaccination during pregnancy was low in Scotland during the predominant delta wave. Consequently, the hospitalizations, including critical care admissions, due to Covid-19 and perinatal mortality, occurred more frequently in those pregnant women who were not vaccinated. (21)

Airborne SARS-CoV2 RNA-containing particles in households:

A study published in the Annals of the American Thoracic Society has for the first time shown that SARS-CoV-2 RNA is present in the airborne particles even outside

the rooms wherein infected persons were in home isolation. A new study has detected tiny airborne particles containing RNA from the SARS-CoV-2 that cause COVID-19, both inside and outside of the rooms in which infected people were self-isolating at home. (22)

Government issues revised COVID-19 treatment guidelines:

The Health Ministry has advised against prescribing steroids to patients with Covid-19 not requiring oxygen supplementation in its updated guidelines for the treatment of Covid-19 citing lack of evidence showing beneficial effects of steroids in these patients. Prescribing high doses of steroids or using them for prolonged duration more than needed or starting steroids too early in the disease may increase the risk of secondary infections such as invasive mucormycosis.

Antiviral Therapy:

Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. The RNA-dependent RNA polymerase of SARS-CoV-2 can serve as a pivot for developing the treatment of coronavirus disease 2019. Molnupiravir, a broad-spectrum antiviral and a prodrug of the nucleoside analogue β -D-N4-hydroxycytidine (NHC) have the potential to increase G to A and C to U transition mutations in reproducing coronaviruses.

Nasal and oral Povidone-Iodine solutions rapidly and effectively inactivate SARS-CoV-2

The ongoing Covid-19 pandemic was first reported in December 2019. Since then it has spread globally

and affected millions of people. Transmission of the severe acute respiratory syndrome-coronavirus 2

(SARS-CoV-2) is via respiratory droplets and contaminated surfaces and objects (fomite transmission).

The reservoirs of the virus are the nasal cavities, nasopharynx, oral cavity and oropharynx.

Use of personal protection equipment (PPE) including masks and regular disinfection of hands

COVID-19 Could be a Risk Factor for New-onset Diabetes in Children:

Children testing positive for COVID-19 may have an increased risk of developing diabetes, suggest new CDC data. An analysis of two different data sources revealed that the risk of being newly diagnosed with diabetes, including type 1, type 2, and other types of diabetes, was significantly higher for those who had COVID-19, in comparison with those who never tested positive. Diabetes incidence was found to be significantly higher among children with the coronavirus infection

Current status of potential therapeutic candidates for the COVID-19 crisis:

Currently, no specific treatment is available for patients with COVID-19 infection. Past management strategies for respiratory viral infections have helped treat COVID-19 in many cases. Numerous potential therapies like supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion are frequently being tried in clinical settings which have rendered some degree of curative benefits in treating patients with COVID-19 infection.

CLINICAL GUIDANCE FOR MANAGEMENT OF ADULT COVID-19 PATIENTS:**(AIIMS and Government of India)**

Adult patient diagnosed with COVID-19

Upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia

Home Isolation & Care:

Physical distancing, indoor mask use, strict hand hygiene Symptomatic management (hydration, antipyretics, antitussive) Stay in Contact with treating physician Monitor temperature and oxygen saturation (by applying a SpO₂ probe to fingers) Seek Immediate Medical Attention If: Difficulty in breathing or SpO₂ <93% High grade fever/severe cough, particularly if lasting for >5 days A low threshold to be kept for those with any of the high-risk features.

High-risk for severe disease or mortality Age > 60 years Cardiovascular disease, hypertension, and CAD Diabetes Mellitus And Other immunocompromised states (such as HIV) Active tuberculosis Chronic lung/kidney/liver disease Cerebrovascular disease Obesity.

Moderate disease

Anyone: 1. Respiratory rate \geq 24/min, breathlessness 2. SpO₂ :90% to \leq 93% on room air

Oxygen Support: Target SpO₂ : 92-96% (88-92% in patients with COPD) Preferred devices for oxygenation: non-rebreathing face mask Awake proning encouraged in all patients requiring supplemental oxygen therapy (se-

quential position changes every 2 hours)

Anti-inflammatory immunomodulatory therapy:

Inj.Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration of 5 to 10 days. Patients may be initiated or switched to oral route if stable and/or improving. There is no evidence for benefit for injectable steroids in those NOT requiring oxygen supplementation, or on continuation after discharge. Anti-inflammatory or immunomodulatory therapy (such as steroids) can have risk of secondary infection such as invasive mucormycosis when used too early, at higher dose or for longer than required. Anticoagulation:

Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (weight based, e.g., enoxaparin 0.5 mg/kg per day SC). There should be no contraindication or high risk of bleeding.

Monitoring:

Clinical Monitoring: breathing rate, Hemodynamic instability, Change in oxygen requirement. Serial CXR; HRCT chest to be done ONLY if there is worsening. **Lab Monitoring:** CRP, D-dimer, blood sugar 48 to 72 hr; CBC, KFT, LFT 24 to 48 hrly.

Severe disease---Any one of: 1. Respiratory rate >30/min, breathlessness 2. SpO₂ <90% on room air

Respiratory support: Consider Use Of NIV (Helmet facemask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW. Consider use of HFNC in patients with increasing oxygen requirement. Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated. Use institutional protocol for ventilatory management when required. Anti-inflammatory immunomodulatory therapy: Inj Methylprednisolone 1 to 2 mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days. Anti-inflammatory or immunomodulatory therapy (such as steroids) can have risk of secondary infection such as invasive mucormycosis when used too early, at higher dose or for longer than required. Supportive measures: Maintain euvolemia (if available, use dynamic measures for assessing fluid responsiveness). If sepsis/septic shock: manage as per existing protocol and local antibiogram. **Monitoring:** Clinical Monitoring: Serial CXR; HRCT chest to be done ONLY if there is worsening. **Lab Monitoring:** CRP, D-dimer, blood sugar 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hourly.

COVID Care:

India is the world's largest democracy having a population of more than 1.2 billion. The covid-19 pandemic has badly affected the country's socio-economic conditions. It was reported that among adults with confirmed COVID-19 infection, 80% experience mild illness, about 14-15% experience moderate-severe disease and 5% are critically ill. The US Centers for Disease Control and Prevention has updated the mask information for Americans and has stated that some masks and respirators provide more protection from COVID-19, compared to others. A CDC statement said that masking is a crucial tool to prevent the spread of COVID-19, and any mask is better than no mask. The update recommends that people of America should wear the most protective mask or respirator that fits well and that they will wear persistently. Masks Can Reduce Distance Airborne Pathogens Travel by More than Half.

The common symptoms:

The common symptoms in both children and adolescents include sore throat, throat irritation, cough, fever, headache, body pains, rhinorrhoea, diarrhoea, Malaise/weakness, and loss of sense of smell and/or taste.

Management protocols:

As per the management protocols developed by the MoHFW for children with acute COVID and MIS-C most of the drugs used in adults such as Ivermectin/HCQ/Favipiravir/Antibiotics such as Doxycycline or Azithromycin are not recommended.

CONCLUSION:

Covid-19, which can manifest as severe acute respiratory failure. Many physicians recognized the emergency demand to fight the challenge. Highly efficacious vaccines now prevail to reduce a vaccinated person's risk of developing symptomatic disease and progressing to require hospital admission. For patients, who are being treated in hospital and require supplemental oxygen, dexamethasone improves survival with additional benefit from Tocilizumab if systemic inflammation is present. With millions of individuals containing COVID-19 worldwide unprecedented number of intensive care unit survivors are now in recovery.

REFERENCES:

- I. Monocentric cohort study, *J Infect Chemother*. 2021 Jun; 27(6): 826–833.
- II. Goyal P., Choi J.J., Pinheiro L.C., Schenck E.J., Chen R. Clinical characteristics of covid-19 in New York city. *N Engl J Med*. 2020;382(24):2372–2374.
- III. Rhodes N.J., Cruce C.E., O'Donnell J.N., Wunderink R.G., Hauser A.R. Resistance trends and treatment options in Gram-negative ventilator-associated pneumonia. *Curr Infect Dis Rep*. 2019;20(2):3.

- IV. Barth R.F., Buja L.M., Parwani A.V. The spectrum of pathological findings in coronavirus disease (COVID-19) and the pathogenesis of SARS-CoV-2. *Diagn Pathol*. 2020;15:85.
- V. Rences, Ozaras R., Cirpin R., Duran A., et al. Influenza and COVID-19 coinfection: report of six cases and review of the literature. *J Med Virol*. 2020; 92(11): 2657–2665.
- VI. König B., König W., Arnold R., Werchau H., Ihorst G., Forster J. Prospective study of human metapneumovirus infection in children less than 3 years of age. *J Clin Microbiol*. 2004; 42(10): 4632–4635.
- VII. Drews A.L., Atmar R.L., Glezen W.P., Baxter B.D., Piedra P.A., Greenberg S.B. Dual respiratory virus infections. *Clin Infect Dis*. 1997; 25(6): 1421–1429.
- VIII. Huang C., Wang Y., Li X., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020; 395(10223): 497–506.
- IX. Lee N., Chan P.K., Yu I.T., et al. Co-circulation of human metapneumovirus and SARS-associated coronavirus during a major nosocomial SARS outbreak in Hong Kong. *J Clin Virol*. 2007; 40(4): 333–337.
- X. Li-Li Ren, Ye-Ming Wang, Zhi-Qiang Wu, Zi-Chun Xiang, Li Guo, Teng Xu, Yong-Zhong Jiang, Yan Xiong, Perlman S., Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol*. 2009; 7:439–50.
- XI. Graham R.L., Baric R.S. Recombination, reservoirs, and the modular spike: mechanisms of coronavirus cross-species transmission. *J Virol*. 2010; 84:3134–46.
- XII. Q. Li et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N. Engl. J. Med*. 382, 1199–1207 (2020).
- XIII. C. Huang et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *Lancet* 395, 497–506 (2020).
- XIV. F. Li, Structure, function, and evolution of coronavirus spike proteins. *Annu. Rev. Virol.* 3, 237–261 (2016).
- XV. S. Perlman, J. Netland, Coronaviruses post-SARS: Update on replication and pathogenesis. *Nat. Rev. Microbiol.* 7, 439–450 (2009).
- XVI. L. Du et al., The spike protein of SARS-CoV—A target for vaccine and therapeutic development. *Nat. Rev. Microbiol.* 7, 226–236 (2009).
- XVII. L. Du et al., MERS-CoV spike protein: A key target for antivirals. *Expert Opin. Ther. Targets* 21, 131–143 (2017).
- XVIII. S. Belouzard, J. K. Millet, B. N. Licitra, G. R. Whittaker, Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* 4, 1011–1033 (2012).
- XIX. T. Heald-Sargent, T. Gallagher, Ready, set, fuse! The coronavirus spike protein and acquisition of fusion competence. *Viruses* 4, 557–580 (2012).
- XX. Stock S.J., et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. 2022 Jan 13. doi: 10.1038/s41591-021-01666-2
- XXI. Laumbach R.J., et al. Presence of SARS-CoV-2 Aerosol in Residences of Adults with COVID-19. *Ann Am Thorac Soc*. 2022 Feb;19(2):338–341. doi: 10.1513/AnnalsATS.202107-847RL.